

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C. 20231  
 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 19 November 1999 (19.11.99)	<b>Applicant's or agent's file reference</b> 2DLST2/99
<b>International application No.</b> PCT/US99/04376	<b>Priority date (day/month/year)</b> 26 February 1998 (26.02.98)
<b>International filing date (day/month/year)</b> 26 February 1999 (26.02.99)	
<b>Applicant</b> McGINNIS, Ralph, Evan et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

24 September 1999 (24.09.99)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland	<b>Authorized officer</b>  Kiwa Mpay
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 26 SEP 2000

WIPO PCT

Applicant's or agent's file reference 2DLST2/99	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/04376	International filing date (day/month/year) 26 FEBRUARY 1999	Priority date (day/month/year) 26 FEBRUARY 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): C12Q 1/68; C07H 21/04 and US Cl.: 435/6, 287.2; 436/94; 536/24.3, 24.31		
Applicant MCGINNIS, RALPH EVAN		

RECEIVED

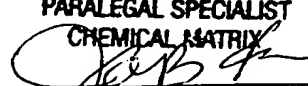
JAN 18 2001

TECH CENTER 1000/2900

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets.  
☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
These annexes consist of a total of 37 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 24 SEPTEMBER 1999	Date of completion of this report 22 MAY 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer KENNETH R. HORLICK Telephone No. (703) 308-0196
Facsimile No. (703) 305-3230	JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX 

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/04376

## I. Basis of the report

## 1. With regard to the elements of the international application:\*

- ☐ the international application as originally filed
- ☒ the description:  
pages \_\_\_\_\_ (See Attached) \_\_\_\_\_, as originally filed  
pages \_\_\_\_\_, filed with the demand  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

- ☒ the claims:  
pages \_\_\_\_\_ (See Attached) \_\_\_\_\_, as originally filed  
pages \_\_\_\_\_, as amended (together with any statement) under Article 19  
pages \_\_\_\_\_, filed with the demand  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

- ☒ the drawings:  
pages \_\_\_\_\_ (See Attached) \_\_\_\_\_, as originally filed  
pages \_\_\_\_\_, filed with the demand  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

- ☒ the sequence listing part of the description:  
pages \_\_\_\_\_ (See Attached) \_\_\_\_\_, as originally filed  
pages \_\_\_\_\_, filed with the demand  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

## 2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

## 3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages \_\_\_\_\_ NONE \_\_\_\_\_
- ☒ the claims, Nos. \_\_\_\_\_ NONE \_\_\_\_\_
- ☒ the drawings, sheets/fig \_\_\_\_\_ NONE \_\_\_\_\_

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\*

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\*Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.  
PCT/US99/04376

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 1 and 2

because:

☐ the said international application, or the said claim Nos. \_ relate to the following subject matter which does not require international preliminary examination (*specify*).

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1 and 2 are so unclear that no meaningful opinion could be formed (*specify*).

No invention is set forth in these claims (claims are too indefinite).

☐ the claims, or said claims Nos. \_ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 1 and 2.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/04376

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement****1. statement**

Novelty (N)	Claims <u>3-96</u>	YES
	Claims <u>none</u>	NO
Inventive Step (IS)	Claims <u>3-96</u>	YES
	Claims <u>none</u>	NO
Industrial Applicability (IA)	Claims <u>3-96</u>	YES
	Claims <u>none</u>	NO

**2. citations and explanations (Rule 70.7)**

Claims 3-96 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the use of CL-F analysis in the study of bi-allelic markers, the CL-F analysis involving a two-dimensional plane having the two orthogonal dimensions of chromosomal location and least common allele frequency.

----- NEW CITATIONS -----

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/04376

**Supplemental B x**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**I. BASIS OF REPORT:**

This report has been drawn on the basis of the description,  
page(s) 1-9, 11-14, 17-32, 35-38 and 40-48, as originally filed.  
page(s) NONE, filed with the demand.  
and additional amendments:  
pages 10, 15, 16, 33, 34 and 39, filed with the letter of 24 May 2000.

This report has been drawn on the basis of the claims,  
page(s) NONE, as originally filed.  
page(s) NONE, as amended under Article 19.  
page(s) NONE, filed with the demand.  
and additional amendments:  
Pages 49-81, filed with the letter of 22 May 2000.

This report has been drawn on the basis of the drawings,  
page(s) 1, as originally filed.  
page(s) NONE, filed with the demand.  
and additional amendments:  
NONE

This report has been drawn on the basis of the sequence listing part of the description:  
page(s) NONE, as originally filed.  
pages(s) NONE, filed with the demand.  
and additional amendments:  
NONE

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/04376

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>														
IPC(6) :C12Q 1/68; C07H 21/04														
US CL :435/6, 287.2; 436/94; 536/24.3, 24.31														
According to International Patent Classification (IPC) or to both national classification and IPC														
<b>B. FIELDS SEARCHED</b>														
Minimum documentation searched (classification system followed by classification symbols)														
U.S. : 435/6, 287.2; 436/94; 536/24.3, 24.31														
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched														
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)														
APS, BIOSIS, CA, MEDLINE search terms:bi-allelic markers, CL-F, frequency, linkage, matrix, chromosome														
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>														
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
A	KRUGLYAK et al. Linkage thresholds for two-stage genome scans. Am. J. Hum. Genet. 1998, Vol. 62, pages 994-996.	2-20, 22-24												
A	KRUGLYAK, L. The use of a genetic map of biallelic markers in linkage studies. Nature Genetics. September 1997, Vol. 17, pages 21-24.	2-20, 22-24												
A	KRUGLYAK et al. Parametric and nonparametric linkage analysis: A unified multipoint approach. Am. J. Hum. Genet. 1996, Vol. 58, pages 1347-1363.	2-20, 22-24												
A	KRUGLYAK et al. Complete multipoint sib-pair analysis of qualitative and quantitative traits. Am. J. Hum. Genet. 1995, Vol. 57, pages 439-454.	2-20, 22-24												
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.														
<table border="0"> <tr> <td>* Special categories of cited documents:</td> <td>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>*A* document defining the general state of the art which is not considered to be of particular relevance</td> <td>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>*E* earlier document published on or after the international filing date</td> <td>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>*L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>*Z* document member of the same patent family</td> </tr> <tr> <td>*O* document referring to an oral disclosure, use, exhibition or other means</td> <td></td> </tr> <tr> <td>*P* document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	*L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family	*O* document referring to an oral disclosure, use, exhibition or other means		*P* document published prior to the international filing date but later than the priority date claimed	
* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention													
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone													
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art													
*L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family													
*O* document referring to an oral disclosure, use, exhibition or other means														
*P* document published prior to the international filing date but later than the priority date claimed														
Date of the actual completion of the international search		Date of mailing of the international search report												
04 MAY 1999		24 MAY 1999												
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer KENNETH R. HORLICK Telephone No. (703) 308-0196												

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/04376

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 1  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
the claim does not set forth an invention
  
3. ☒ Claims Nos.: 21 and 25  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.





## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification<sup>6</sup> :

C12Q 1/68, C07H 21/04

A1

(11) International Publication Number:

WO 99/43858

(43) International Publication Date:

2 September 1999 (02.09.99)

(21) International Application Number: PCT/US99/04376

(22) International Filing Date: 26 February 1999 (26.02.99)

## (30) Priority Data:

60/076,102	26 February 1998 (26.02.98)	US
60/076,182	27 February 1998 (27.02.98)	US
60/086,947	27 May 1998 (27.05.98)	US
60/107,673	7 November 1998 (07.11.98)	US

## (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications

US	60/076,182 (CIP)
Filed on	27 February 1998 (27.02.98)
US	60/086,947 (CIP)
Filed on	27 May 1998 (27.05.98)
US	60/076,102 (CIP)
Filed on	26 February 1998 (26.02.98)
US	60/107,673 (CIP)
Filed on	7 November 1998 (07.11.98)

(71)(72) Applicants and Inventors: McGINNIS, Ralph, Evan [US/GB]; 27 Ladywell Prospect, Sawbridgeworth, Herts CM21 9PR (GB). McGINNIS, Robert, Owen [US/US]; 1575 West Kagy Boulevard, Bozeman, MT 59715 (US).

(74) Common Representative: McGINNIS, Robert, Owen; 1575 West Kagy Boulevard, Bozeman, MT 59715 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

## Published

With international search report.

With amended claims and statement.

(54) Title: TWO-DIMENSIONAL LINKAGE STUDY TECHNIQUES

## (57) Abstract

Versions of the invention are directed to methods (including software), apparatus, compositions of matter, and new uses of compositions of matter for a new type of association based linkage study technique using bi-allelic markers. In this new type of association based linkage study technique, the bi-allelic markers used in the new linkage studies are chosen so that the least common allele frequencies of the markers vary systematically over a range or subrange of least common allele frequency and the chromosomal location of the markers vary systematically over one or more chromosomes or chromosomal regions. And the bi-allelic markers are chosen so that the markers' chromosomal locations and least common allele frequencies vary systematically in an essentially independent manner. This selection of markers achieves a systematic distribution of the markers over a two-dimensional region having the orthogonal dimensions of chromosomal location and least common allele frequency. By using the two characteristics or two dimensions of marker chromosomal location and marker allele population frequency in this unique way, the power and systematic nature of genetic linkage studies using association based linkage tests is greatly increased. These unique two-dimensional linkage study techniques increase the power of association based linkage studies to localize trait causing genes or polymorphisms of modest effect such as human disease causing polymorphisms.